Pharmacokinetics of Thallium-201 in Normal Individuals After Routine Myocardial Scintigraphy

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Data of pharmacokinetic distribution of and radiation dose from ^{201}Tl chloride used in routine myocardial scintigraphy are based on animal studies or on small groups of humans not exercised. In order to obtain data under routine conditions pharmacokinetics of ^{201}Tl were measured in 15 individuals who had undergone diagnostic myocardial scintigraphy and were classified as normal. Ventral and dorsal whole-body scans were acquired until 9 days after injection. Conjugate pixels were averaged geometrically. Percentage values of total administered dose were obtained for total body and 13 organs by using a calculation method that takes into account the differentiation of overlapping organs.

J Nucl Med 29:1582–1586, 1988

The use of radioactive thallium in nuclear medicine was first suggested by Kawana et al. in 1970 (*1*). Three years later Lebowitz et al. introduced thallium-201 (^{201}Tl) to myocardial scintigraphy (*2,3*). Thallium is a potassium analog in terms of organ distribution and neurophysiological function (*4–6*). Although ^{201}Tl is a radiopharmaceutical used in routine nuclear medicine there have been few studies on pharmacokinetic distribution. Those animal data from which biodistribution in man were derived showed large discrepancies (*7–9*). Only small groups of patients (e.g., n = 4) were investigated in the very few measurements so far carried out in man. Furthermore the patients were not exercised, unlike the current procedure of myocardial investigation with ^{201}Tl. The purpose of the study presented here was to measure the spatial and temporal distribution ^{201}Tl in patients after a routine diagnostic myocardial study, so that values of radiation dose could be calculated. Based upon considerations by Budinger (*10*) and Sorenson (*11*) about whole-body scanning a simple method of whole-body measurement was developed for absolute quantification of ^{201}Tl distributed in man.

Received Dec. 12, 1986; revision accepted Mar. 28, 1988.

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MATERIALS AND METHODS

Patients in whom the pharmacokinetic distribution of ^{201}Tl was measured were chosen from those patients who were checked for ischemic heart disease by normal myocardial scintigraphy in our nuclear medical department. Myocardial scintigraphy was preceded by bicycle exercise beginning with a load of 25 W and ending with maximal exercise after stepwise increasing the load by 25 W every 2 min. At maximal exercise 74 MBq (2 mCi) [^{201}Tl]chloride were injected intravenously. Immediately afterwards and 3 hr later planar or SPECT scintigraphic studies were acquired.

Candidates for the pharmacokinetic measurements were patients with nonspecific symptoms of angina, no history of ischemia and no abnormal findings in diagnostic evaluation by myocardial scintigraphy. The pharmacokinetic measurements were carried out in 15 patients (14 male, one female) aged 41 to 62 yr. Ventral and dorsal whole-body scans were acquired at ~2, 24, 48, 120, 168, and 216 hr after injection. The scans were obtained using a Searle-LFOV gamma camera with a movable whole-body scan table and a high resolution parallel collimator. Scan data were stored and evaluated using a mini-computer-system with appropriate nuclear medical application software.

In order to quantify the distribution of ^{201}Tl the ventral and dorsal (e.g., conjugate) whole-body scans were geometrically averaged pixel by pixel. Errors caused by count statistics were reduced by 4-2-1 weighted 9-point smoothing before averaging. The distribution of activity is related to the geometric mean of counts measured from ventral and dorsal views

according to the following equation (*10,11*):

$$A_0 = G\,(N_V\,N_D)^{1/2}\,e^{(\mu/2)L}\,\frac{\mu d/2}{\sinh(\mu d/2)} \qquad (1)$$

with

A_0: Activity represented in one pixel
G: Constant of measurement device involving efficiency etc,
N_V, N_D: Count rate per pixel in ventral or dorsal view,
μ: Absorption coefficient at pixel of interest (POI),
L: Body thickness at POI,
d: Organ thickness at POI.

The main reason for using this relationship is the exclusion of the unknown depth of the location of the activity. Myers et al. (*12*) showed that the term involving the organ thickness d is close to one, so that an exact calculation of this term is not necessary. The absorption factor $e^{(\mu/2)L}$ includes the unknown variable μ and the externally measurable (but variable) body thickness L. This factor might be determined by a whole-body transmission scan before the injection. For each emission scan the patient must be repositioned exactly. In order to simplify the procedure relative absorption factors were determined in several volunteers by transmission measurements using a ^{201}Tl-filled flood phantom. For head, heart, and abdomen the relative absorption factors were set to one. These transmission measurements yielded the factors 0.5 for neck and legs, 0.4 for thorax (without heart), and 0.33 for arms. In this way the individual thickness and/or absorption coefficient of these parts of the body were taken into account. The inhomogeneous thickness of the trunk was corrected for by assuming its cross section to be elliptical. In this calculation a measured effective absorption coefficient of 0.149 cm^{-1} was used. After calculation of the geometrically averaged count rate in each pixel (N_{GA}) the multiplicative correction was performed for the regions of trunk, arms, legs, neck, and thorax. Thus a corrected count rate (N_{GAC}) for each pixel of the patient's scan is obtained. This count rate is assumed to be proportional to the activity underlying the single pixels. The activity A_i of a particular organ i relative to the whole-body activity A_{ges} is given by:

$$A_i = A_{ges}\,\frac{\sum_i N_{GAC}}{\sum_{ges} N_{GAC}} \qquad (2)$$

with

$\sum_i N_{GAC}$: Sum of corrected pixel count rates over organ i
$\sum_{ges} N_{GAC}$: Sum of corrected pixel count rates over whole-body.

In order to determine the uptake in two organs overlapping in one region, one of which is ventrally and the other dorsally located (e.g., liver and right kidney, or stomach and left kidney), the following procedure was developed. A_{VD}, the total activity of the overlapping organs, is first calculated using Eq. (2), with A_V the activity of the ventrally located organ and A_D the activity of the dorsally located organ. As ^{201}Tl has a low photon energy with a rather high absorption coefficient it is assumed that a count rate N_V measured from a ventral view mainly originates from the activity A_V. This is explained by the following calculation: with the absorption coefficient of 0.149 cm^{-1} of ^{201}Tl, an assumed depth of 5 cm of the ventral organ and an assumed depth of 15 cm of the dorsal organ the ratio of counts from these organs measured from a ventral view is 1:0.21. If the counts from the dorsal organ are neglected, it follows

$$N_V = G\,A_V\,e^{-(\mu l_V)}. \qquad (3)$$

The corresponding relationship is used for N_D and A_D:

$$N_D = G\,A_D\,e^{-(\mu l_D)}. \qquad (4)$$

Because the depths l of the organs under consideration (liver versus right kidney, stomach versus left kidney) are not very different, l_V and l_D are assumed to be equal.
Therefore it follows that

$$\frac{N_V}{N_D} = \frac{A_V}{A_D} \qquad (5)$$

and with

$$A_{VD} = A_V + A_D \qquad (6)$$

$$A_V = \frac{N_V\,A_{VD}}{N_V + N_D} \qquad (7)$$

and

$$A_D = \frac{N_D\,A_{VD}}{N_D + N_V}. \qquad (8)$$

Liver and stomach uptake were calculated according to Eq. (7) and kidney uptake according to Eq. (8). All count rates were corrected for physical decay. The whole-body count rate $\sum_{ges} N_{GAC}$ of the first whole-body measurement at 2 hr p.i. (= N_0) is considered to represent the original whole-body activity A_{ges} which is the total administered dose (TAD) and is set equal to 100%. Between the injection and the first whole-body scan there was no loss of urine. All whole-body activities of later measurements and all organ activities are related to N_0 so that they are expressed as percent TAD.

The quantification procedure described here was examined by a test with an anthropomorphic whole-body Alderson phantom. All compartments of this phantom were filled with known amounts of [^{201}Tl] chloride so that an activity distribution similar to the one expected in the human body was achieved. Based upon the activity data dosis calculation was performed separately for each individual according to the MIRD Pamphlet No. 11 (*13*). From the source organs listed in this paper liver, stomach, kidneys, spleen, thyroid, intestine, and testes were considered for this calculation. The accumulated activities in the segments of intestine are calculated from the activity given for the total intestine according to ICRP Publication No. 30 (*14*). Other source organs like legs, arms, and thorax, in which substantial amounts of activity were found, were considered by summing up these activities for the rest body. In order to give a dose estimate for the total body the effective dose equivalent was used, which is defined by ICRP Publication No. 26 (*15*) as the weighted sum of organ doses thus taking into account the individual risks of different organs.

RESULTS

In test measurements with the Alderson phantom errors were calculated as differences between the activities determined by the quantitation method described above and the true activities in the "organs." The errors ranged between 1.8% and 13.3% with an average value of 5.2%. For the overlapping organs liver, stomach, and kidneys errors were from 6.3% to 13.3%.

The mean values for whole-body and organ activities measured from 2 hr p.i. until 9 days p.i. in 15 normal individuals are summarized in Table 1. All data are percent values related to the whole-body activity at 2 hr p.i., which represents TAD. Some organs are listed totally and in part, so that the sum of all organs mentioned is >100%. The heart which is the organ of diagnostic interest has an uptake between only 3.9% TAD at 2 hr p.i. and 1.5% TAD at 9 days p.i. The brain is the organ with the highest relative increase of activity from 1.46% TAD at 2 hr p.i. to 2.08% TAD at 5 days p.i. Afterwards brain activity decreases.

The effective half-life of whole-body activity was found to be 58.8 ± 4.2 hr. From this figure and the physical half-life of 73.1 hr a biologic half-life of 12.5 days is calculated.

The relationship between uptake of ^{201}Tl in the femoral musculature and the load of maximum exercise could be studied in eight of 15 patients. Figure 1 shows an increase of uptake in this musculature in direct relation to the load. The correlation coefficient of this relationship is 0.93 ($p < 0.001$).

Table 2 gives the mean values of radiation dose for single organs and the mean effective dose equivalent. The lower large intestine with a dose of 0.15 mGy/MBq is determined as the critical organ. It is followed by thyroid and testes with ~0.09 mGy/MBq. The radiation dose to the heart is only 0.009 mGy/MBq.

DISCUSSION

The method for quantifying activity in two overlapping organs involves special problems. First, the organs are not of equal size and do not overlap totally. Second, the assumption that ventrally and dorsally situated organs lie at the same depth from their nearest surface ($l_V = l_D$) is only a rather rough estimation. These problems exist for the measurements both in the Alderson phantom and in humans. In spite of these difficulties the relative errors of the Alderson test for liver, stomach, and kidney range from 6.3% to only 13.3%. These errors are considered to be estimates for the resulting errors in patient measurements. Although the total activity and its distribution were similar in phantom and patients, these errors may be increased by uncertainties in defining regions of interest, fixed transmission factors, and the assumption of an elliptical cross section of the trunk.

The mean effective half-life of ^{201}Tl whole-body activity is 58.8 hr and is nearly equal to the 57 hr value given by Atkins et al. (*16*) and the 57.1 hr value given by Samson et al. (*17*).

Findings in rats by Kamerbeek et al. (*18,19*) and Rauws (*20*) of an increase of brain activity during the

TABLE 1

Organ	Time after injection (hr)*					
	2	24	48	120	168	216
Whole-body	100.0	95.1 ± 2.7	90.5 ± 3.0	75.3 ± 5.7	68.7 ± 6.5	63.3 ± 7.4
Brain	1.5 ± 0.3	1.7 ± 0.3	1.8 ± 0.3	2.1 ± 0.2	1.9 ± 0.3	1.8 ± 0.2
Facial part	3.1 ± 0.5	3.2 ± 0.4	3.2 ± 0.5	2.9 ± 0.4	2.7 ± 0.5	2.3 ± 0.3
Neck	1.2 ± 0.2	1.2 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	0.8 ± 0.2	0.7 ± 0.2
Thyroid	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Heart	3.9 ± 0.9	2.9 ± 0.6	2.6 ± 0.4	2.1 ± 0.3	1.8 ± 0.3	1.5 ± 0.4
Thorax (without heart)	6.2 ± 0.6	6.1 ± 0.5	5.8 ± 0.6	4.7 ± 0.6	4.1 ± 0.6	3.5 ± 0.7
Liver	5.1 ± 0.7	4.1 ± 0.5	3.8 ± 0.3	3.1 ± 0.4	2.7 ± 0.3	2.4 ± 0.3
Stomach	3.2 ± 0.5	2.5 ± 0.5	2.2 ± 0.4	1.8 ± 0.3	1.6 ± 0.3	1.5 ± 0.3
Spleen	1.0 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Intestine	20.1 ± 2.2	20.7 ± 1.7	19.7 ± 1.7	15.2 ± 2.0	13.0 ± 2.0	10.7 ± 2.4
Kidneys	5.6 ± 1.4	4.6 ± 0.8	4.2 ± 0.6	3.4 ± 0.6	3.0 ± 0.4	2.5 ± 0.5
Arms	5.1 ± 0.9	6.7 ± 1.0	6.7 ± 0.9	5.8 ± 0.9	5.3 ± 0.8	5.0 ± 0.9
Legs	26.2 ± 4.0	23.0 ± 2.2	21.0 ± 2.3	17.3 ± 2.0	15.9 ± 2.0	15.4 ± 1.6
Thigh	18.2 ± 2.4	15.0 ± 1.5	13.2 ± 1.6	10.5 ± 1.4	9.5 ± 1.3	9.3 ± 0.9
Lower leg, foot	7.7 ± 1.8	8.1 ± 1.2	7.8 ± 0.9	6.8 ± 0.8	6.4 ± 0.7	6.0 ± 0.7
Femoral muscles	16.3 ± 2.2	13.1 ± 1.5	11.4 ± 1.5	9.1 ± 1.2	8.1 ± 1.2	8.0 ± 0.8
Tibial muscles	5.9 ± 1.4	5.7 ± 0.9	5.5 ± 0.7	4.6 ± 0.6	4.3 ± 0.5	4.2 ± 0.5
Testis (n = 14)	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1

* Mean and standard deviation of the whole-body and relative organ activities in 15 patients (percentage data, corrected for decay).

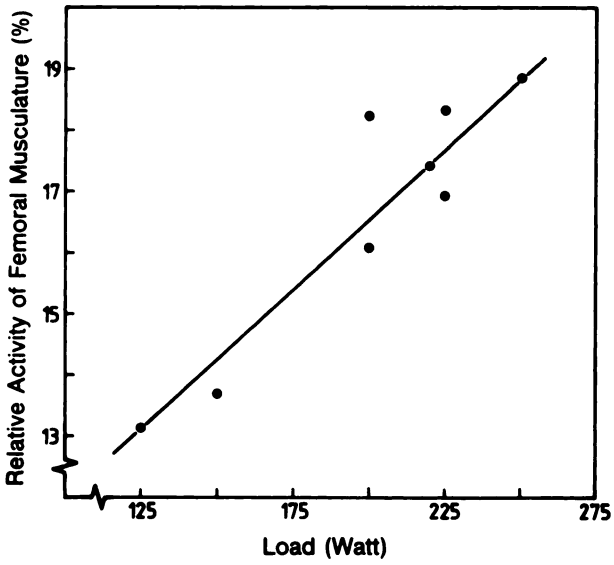

FIGURE 1
Relationship between ^{201}Tl uptake in the femoral muscles and the load during exercise

first days p.i. are confirmed by our data that shown an increase of brain activity from 1.46% TAD at 2 hr p.i. to 2.08% TAD at 5 days p.i. In the thorax (heart included) an activity of 10% TAD was found similar to a value determined by Atkins et al. (*16*). In the heart region a mean uptake of 3.9% TAD was measured at 2 hr p.i. The heart uptake of 3.6% TAD which Samson et al. (*17*) determined by autopsy is nearly the same, whereas Atkins et al. (*16*) found a figure of only 1% TAD in patients not exercised. Myocardial uptake of ^{201}Tl is dependent on the mass of muscle and perfusion, which is increased according to the load (*21–24*). This relationship is also true for the skeletal muscles. Siegel and Stewart (*25*) described an increased uptake in the legs after bicycle exercise. In concordance we found the highest uptake of ^{201}Tl in the legs and especially in the femoral musculature, which does the main work during exercise.

Relative to the washout of whole-body activity an increased washout is found in heart, liver, kidneys, stomach, and upper legs whereas a decreased washout is found in brain, intestine, arms, and testes. This indicates a redistribution of ^{201}Tl in the body during the period of 9 days after injection considered by this study.

The uptake in the red marrow was not directly measured. Its radiation dose is estimated via the activity of the rest body for which a homogeneous distribution was assumed. The calculation of radiation dose determines the intestine as the organ with the highest dose, as it was obtained by Samson et al. (*17*). Although Atkins et al. (*16*) found organs with higher dose, the intestine value determined by him is in the same range. The radiation dose of all other organs are partly considerably lower than the data given by those two authors (*16,17*).

TABLE 2

Organ	Radiation dose* mGy/MBq	Radiation dose* rad/mCi
Adrenals	0.0105 ± 0.0020	0.0389 ± 0.0074
Bladder wall	0.0120 ± 0.0024	0.0443 ± 0.0090
Bone	0.0128 ± 0.0026	0.0472 ± 0.0098
Heart	0.0089 ± 0.0014	0.0329 ± 0.0052
GI tract		
Small intestine	0.0165 ± 0.0028	0.0609 ± 0.0103
Upper large intestine	0.0703 ± 0.0203	0.2601 ± 0.0753
Lower large intestine	0.1451 ± 0.0441	0.5367 ± 0.1633
Kidney	0.0638 ± 0.0108	0.2361 ± 0.0400
Liver	0.0145 ± 0.0021	0.0537 ± 0.0078
Lungs	0.0092 ± 0.0020	0.0340 ± 0.0072
Red marrow	0.0171 ± 0.0034	0.0632 ± 0.0125
Muscle	0.0092 ± 0.0019	0.0342 ± 0.0070
Pancreas	0.0133 ± 0.0026	0.0492 ± 0.0095
Skin	0.0068 ± 0.0014	0.0250 ± 0.0053
Spleen	0.0268 ± 0.0073	0.0991 ± 0.0269
Stomach wall	0.0283 ± 0.0071	0.1046 ± 0.0264
Testes (n = 14)	0.0908 ± 0.0578	0.3359 ± 0.2138
Thyroid	0.0923 ± 0.0234	0.3413 ± 0.0867
Uterus (n = 1)	0.0135	0.0499
Eff. dose equivalent	0.0961 ± 0.0476 (mSv/MBq)	0.3555 ± 0.1762 (rem/mCi)

* Radiation doses (mean ± s.d.) to various organs and effective dose equivalent after intravenous injection of [^{201}Tl]chloride (n = 15).

ACKNOWLEDGMENTS

The authors acknowledge the help of Mr. U. Elsasser (Inst. fuer Strahlen-hygiene, Bundesgesundheitsamt, Neuherberg, F.R.G.) in calculating the radiation dose and the critical support of Prof. D.D. Patton (Tuscon, Arizona, USA) in preparing the manuscript and the secretarial help of Mrs. D. Beaujean and Mrs. Ch. Behrendt.

This study was supported in part by the Ministry of the Interior (Grant BMI St.Sch. 757f).

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